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# Continuous representations of brain connectivity using spatial point processes

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ABSTRACT

We present a continuous model for structural brain connectivity based on the Poisson point process. The model treats each streamline curve in a tractography as an observed event in connectome space, here the product space of the gray matter/white matter interfaces. We approximate the model parameter via kernel density estimation. To deal with the heavy computational burden, we develop a fast parameter estimation method by pre-computing associated Legendre products of the data, leveraging properties of the spherical heat kernel. We show how our approach can be used to assess the quality of cortical parcellations with respect to connectivity. We further present empirical results that suggest that "discrete" connectomes derived from our model have substantially higher test-retest reliability compared to standard methods. In this, the expanded form of this paper for journal publication, we also explore parcellation free analysis techniques that avoid the use of explicit partitions of the cortical surface altogether. We provide an analysis of sex effects on our proposed continuous representation, demonstrating the utility of this approach.



## 1. Introduction

In recent years the study of structural and functional brain connectivity has expanded rapidly. Following the rise of diffusion and functional MRI, connectomics has unlocked a wealth of knowledge to be explored. Almost synonymous with the connectome is the network-theory based representation of the brain (Sporns et al., 2000). In much of the recent literature the quantitative analysis of connectomes has focused on region-to-region connectivity. This paradigm equates physical brain regions with nodes in a graph, and uses observed structural measurements or functional correlations as a proxy for edge strengths between nodes.

Critical to this representation of connectivity is the delineation of brain regions, the parcellation. Multiple studies have shown that the choice of parcellation influences the graph statistics of both structural and functional networks (Van Wijk et al., 2010; Zalesky et al., 2010; Satterthwaite and Davatzikos, 2015; Wang et al., 2009). It remains an open question which of the proposed parcellations is the optimal representation, or even if such a parcellation exists (de Reus and Van den Heuvel, 2013).

It is thus useful to construct a more general framework for cortical connectivity, one in which any particular parcellation of the cortex may be expressed and its connectivity matrix derived, and one in which the variability of connectivity measures can be modeled and assessed statistically. It is also important that this framework allow comparisons between parcellations, and representations in this framework must be both analytically and computationally tractable. Since several brain parcellations at the macroscopic scale are plausible, a representation of connectivity that is independent of parcellation is particularly appealing.

In this paper, we develop such a general framework for a parcellation independent connectivity representation, building on the work of Gutman et al. (2014). We describe a continuous point process model for the generation of observed tract[1] (streamline) intersections with the cortical surface, from which we may recover a distribution of edge strengths for any pair of cortical regions, as

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[1] It is critical to distinguish between white matter fibers (fascicles) and observed "tracts." Here, "tracts" denotes the 3d-curves recovered from Diffusion Weighted Imaging via tractography algorithms.

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measured by the inter-region tract count. Our model is an intensity function over the product space of the cortical surface with itself, assigning to every pair of points on the surface a connectivity density, opposed to the usual connectivity mass assigned in discrete models. We describe an efficient method to estimate the parameter of the model, as well as a method to recover the region-to-region edge strength. We then demonstrate the estimation of the model on a test-retest dataset. We provide reproducibility estimates for our method and the standard direct count method (Jahanshad et al., 2013) for comparison. We also compare the representational power of common cortical parcellations with respect to a variety of measures.

In this, the extended journal form of the conference publication (Moyer et al., 2016), we explore possible methods for direct analysis of the continuous connective object. We present an exemplar analysis of group differences in continuous summary measures (regressing a connectivity measure on sex, with age and ICV covariates), showing significant differences in regions also identified using parcellation-based representations. We use this analysis to demonstrate a practical analysis of the proposed model.

## 2. Continuous connectivity model

The key theoretical component of our work is the use of point process theory to describe estimated cortical tract projections. A point process is a random process where any realization consists of a collection of discrete points on a measurable space. The most basic of these processes is the Poisson process, in which events occur independently at a specific asymptotic intensity (rate) $\lambda$ over the chosen domain (Moller and Waagepetersen, 2003). $\lambda$ completely characterizes each particular process, and is often defined as a non-negative function $\lambda : \text{Domain} \to \mathbb{R}^+$, which allows the process to vary in intensity by location. This is functionally similar to a probability density, except that realizations of the Poisson process can consist of zero, one, or many points, the points are independent by assumption, and $\lambda$ need not integrate to one.

The expected count of any sub-region (subset) of the domain is its total intensity, the integral of $\lambda$ over the sub-region. In this paper, our domain is the connectivity space of the cortex, the set of all pairs of points on the surface, and the events are estimated tract intersections with the cortical surface.

### 2.1. Model definition and properties

Let $\Omega$ be union of two disjoint subspaces each diffeomorphic to the 2-sphere representing the white matter boundaries in each hemisphere. Further consider the space $\Omega \times \Omega$, which here represents all possible endpoint pairs for tracts that reach the white matter boundary. We denote the set of observed tract endpoint pairs as $D$. We treat the observation of such tracts as events generated by an inhomogeneous (symmetric) Poisson process on $\Omega \times \Omega$; in our case, for every event $(x, y)$ we have a symmetric event $(y, x)$.

Assuming that each event is independent of all other events except for its symmetric event (i.e., each tract in $D$ is recovered independently), we model connectivity as a intensity function $\lambda : \Omega \times \Omega \to \mathbb{R}^+$, such that for any regions $E_1, E_2 \subset \Omega$, the number of events is Poisson distributed with parameter

$$\mathcal{C}(E_1, E_2) = \iint_{E_1, E_2} \lambda(x, y) dx dy. \tag{1}$$

Due to properties of the Poisson distribution, the expected number of tracts is exactly $\mathcal{C}(E_1, E_2)$. For any collection of regions $\{E_i\}_{i=1}^N = P$, we can compute a weighted graph $\mathcal{G}(P, \lambda)$ by computing each $\mathcal{C}(E_i, E_j)$ for pairs $(E_i, E_j) \in P \times P$. Each node in this graph is an element of $P$ (a subset of $\Omega$, a region of the cortical surface), and the edges between them are the rate at which we observe streamlines between the regions.

We call $P$ a parcellation of $\Omega$ if $\bigcup_i E_i = \Omega$ and $\bigcap_i E_i$ has measure zero ($\{E_i\}$ is almost disjoint). If $P$ is a parcellation, then $\mathcal{G}(P, \lambda)$ has Poisson rate parameters as edges. For any realization of endpoints, the count matrices that form traditional connectomes are independent draws from Poisson distributions with elements of $\mathcal{G}(P, \lambda)$ as parameters. The independence of the observations is conditional on $\lambda$ and the fact that $P$ is a parcellation, and does not imply an independence of the rates of the different regions—in other words, the observed counts are independent given the parameters, but this model does not speak to the generation of the parameters themselves.

It is immediately clear that $\lambda$ is one such parcellation independent representation of connectivity that we desired in Section 1. $\lambda$ is defined without reference to any particular parcellation; moreover, for any choice of parcellation $P$ or even more general sets of subsets of $\Omega$ (e.g. overlapping sets) we can recover the parameters of a random network $\mathcal{G}(P, \lambda)$. While $\lambda$ is a representation of cortical connectivity, we posit that $\lambda$ itself is not a weighted graph as it no longer has a countable set of nodes. However, it does retain several graph-like constructions, namely a function analogous to weighted-degree ("strength").

Define the marginal connectivity over a region $E \subset \Omega$ as $M(\cdot; E) : \Omega \to \mathbb{R}^+$ as:

$$M(x; E) = \int_E \lambda(x, y) dy. \tag{2}$$

This is the aggregate connectivity to any point in region $E_i$ from any point $x$–the pointwise intensity of observing a tract incident on $x$ for which the other endpoint is contained in $E_i$. Further define

$$M(x) = M(x; \Omega) = \int_\Omega \lambda(x, y) dy. \tag{3}$$

This is the direct analogue of the sum of the edge weights for a given node $x$, i.e. the weighted degree. It is equal to the pointwise rate at which tracts are incident on $x$, connecting to any other point. If $\lambda$ is continuous, then it can be shown that $M(x)$ is also continuous.

### 2.2. Selection of a parcellation

$\mathcal{G}(P, \lambda)$ is a summary statistic for the intensity function $\lambda$, in that it summarizes information about the rate of tract observation into a finite set of scalars. It is clearly dependent on the parcellation $P$. Thus, given $\lambda$ and two or more parcellations $P_1, P_2, \ldots$, we would like to know which parcellation and associated summary statistic (graph) $\mathcal{G}(P, \lambda)$ best represents the underlying connectivity function. This requires a definition of the goodness of a representation; in practical terms, this means we need to choose a loss function in order to quantify how well $\mathcal{G}(P, \lambda)$ represents $\lambda$. There are at least two perspectives to consider, one in which $\mathcal{G}(P, \lambda)$ is viewed as an approximation to the function $\lambda$, and another in which $\mathcal{G}(P, \lambda)$ is viewed as an approximation to the parameter of the point process model.

$L^2$ Approximation Error: Because each $P_i$ covers $\Omega$ (and $P_i \times P_i = \Omega \times \Omega$), each $\mathcal{G}(P_1, \lambda)$ can be viewed as a piece-wise function $g : \Omega \times \Omega \to \mathbb{R}^+$, where $g(x, y) = \frac{1}{|E_i||E_j|}\mathcal{C}(E_i, E_j)$ such that $x \in E_i$ and $y \in E_j$. In other words, $g$ is the constant approximation to $\lambda$ over every pair of regions. A natural measure of error is another form of Integrated Squared Error:

$$Err(\lambda, \mathcal{G}(P_1, \lambda)) = \iint_{\Omega \times \Omega} (g(x, y) - \lambda(x, y))^2 dx dy. \tag{4}$$

This is analogous to squared loss ($\ell_2$-loss).

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